

Review Article

Introduction of Polymer Nanoparticles for Drug Delivery Applications

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Abstract

The past half of a century has seen increasing attention focused on the development of polymer nanoparticle based drug delivery systems as being capable of improving the efficacy and obviating the systematic side effects of a wide range of antineoplastic drugs in human cancer therapy. This has led to the emergence of multifunctional “smart” nanoparticles for carrying out protective polymer capping, targeting ligand, diagnostic label, stimuli-sensitive segments, image contrast agent, and other demanding functional groups. In this article we introduce the basic knowledge and general features of polymer nanoparticles for the purpose of drug delivery. In addition, various types of polymer nanoparticles used in drug delivery systems are presented. The criteria for the development of the required polymer nanoparticles is also summarized.

Keywords: Biodegradable polymer; Controlled release; Drug delivery; Liposome; Polymer nanoparticles; Stimuli responsiveness

Background

The essence of “nano-” science and technology is based on the finding that the properties of materials over the size range of 1-100 nm differ from those of the bulk material. The unique properties of these various types of intentionally produced nanomaterials provide them with novel electrical, catalytic, magnetic, mechanical, thermal, and imaging features that are highly desirable for applications in commercial, medical, military, and environmental sectors. These materials may also find their way into more complex nanostructures and systems. As new uses for materials with these special properties are identified, the number of products containing such nanomaterials and their possible applications continues to grow.

In the fields of molecular biology and medicine, cancer has been the leading cause of death and a serious threat to the body health of

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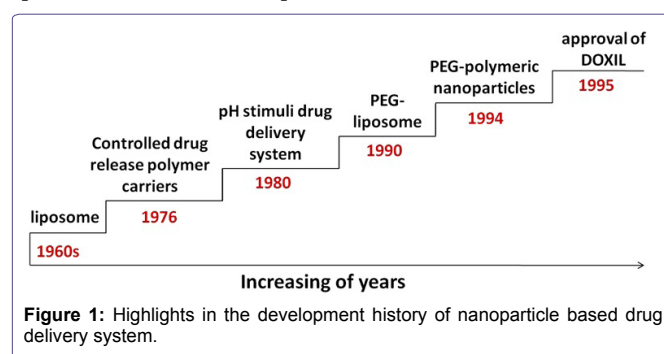
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human beings. Until now, the main techniques to fight cancer are non-targeted chemotherapy and radiation. However, it is unavoidable to prevent systematic side effects to the human body due to non-specific uptake by normal, healthy, noncancerous tissues because of the instinctive properties of the chemotherapy chemical agent featured with high toxicity and a lack of tumor specificity.

In order to overcome the limitations of free chemotherapeutic agents, targeting of tumors with nanoparticulate drug carriers has received much attention and expectance [1,2]. Nanocarriers can offer many avenues over free drugs for the following aspects [3]: (1) protect the drug from premature degradation; (2) prevent drugs from prematurely interacting with the biological environment; (3) enhance absorption of the drugs into a selected tissue (for example, solid tumour); (4) control the pharmacokinetic and drug distribution profile; and (5) improve intracellular penetration.

Let us first recall the important moments in the short but rapid development history of drug delivery systems (Figure 1). Lipid is the first nanotechnology based drug delivery system, which was discovered in the 1960s and later known as liposomes [4]. After that, biomaterials made of a variety of organic and inorganic substances were developed for drug delivery. In 1976, the first controlled release polymer drug delivery system was reported [5]. In 1980, pH stimuli drug delivery systems to trigger drug release [6] and cell specific targeting of liposomes were reported [7,8]. In 1987, the first long circulating liposome named “stealth liposomes” was described [9]. Subsequently, the use of Polyethylene Glycol (PEG) was known to increase circulation times for liposomes [10] and polymer nanoparticles [11] in 1990 and 1994, respectively, which established a solid foundation for the development and subsequent approval of DOXIL (Doxorubicin Liposome) in 1995 for the treatment of epidemic (AIDS-related) Kaposi sarcoma [12].



After fifty-years of development of drug delivery systems, biocompatible polymer nanoparticles have been regarded as a substantial promising effective drug delivery system characterized by the self-assembly of amphiphilic block copolymer surfactants (frozen micelles), dendrimers, vesicles, liposome, emulsions, microemulsion, and latex particles. Drug delivery systems based on polymer nanoparticles generally have the following properties [13-17]: (1) decreased immunogenicity; (2) protection from alteration and inactivation of the active drug; (3) altered biodistribution to reduce systemic toxicity; (4) elimination of multidrug resistance;

(5) increased tumor cytotoxicity; (6) passive targeting by Enhanced Permeability and Retention (EPR); and (7) site-specific delivery of drugs by active targeting. On the other hand, in order to reach the rapid and effective clinical translation, these nanocarriers must (1) be made from a material that is biocompatible, well characterized, and easily functionalized; (2) exhibit high differential uptake efficiency in the target cells over normal cells or tissue; (3) be either soluble or colloidal under aqueous conditions for increased effectiveness; and (4) have an extended circulating half-life, a low rate of aggregation, and a long shelf life.

Biodegradable Polymers

Biodegradable polymers used in drug delivery studies can be broadly classified into two categories: natural and synthetic polymers. The majority of investigations into the use of natural polymers as drug delivery systems have concentrated on the use of proteins such as collagen, gelatin, insulin, and albumin and polysaccharides such as starch, dextran, cellulose, and hyaluronic acid.

Various synthetic degradable polymers have been reported for the formulation of controlled drug delivery systems, since they can be synthesized with specific properties to meet particular applications. Probably the most widely investigated biodegradable synthetic polymers are linear aliphatic polyesters Poly (Lactic Acid) (PLA), Poly (Glycolic Acid) (PGA), Poly (Lactic Acid-co-Glycolide) (PLGA), and Poly (ϵ -Caprolactone) (PCL). They exhibit important advantages of biocompatibility, predictability of biodegradation kinetics, ease of fabrication, and regulatory approval.

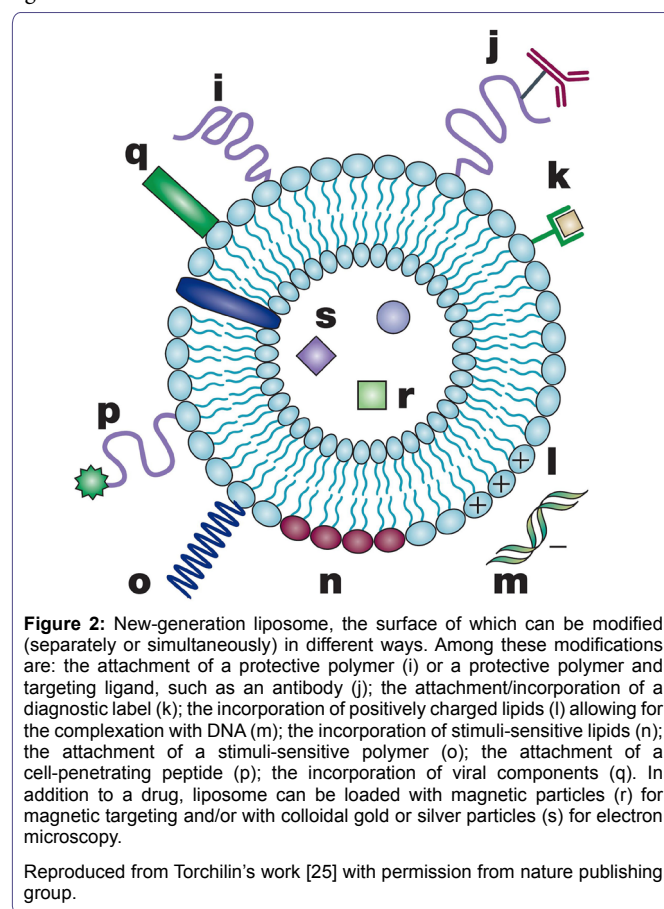
Polyanhydride polymers and copolymers have also received considerable interest for the preparation of drug delivery systems due to their labile anhydride linkages in the polymer structure. In addition, poly (ortho ester)'s and polyphosphazenes have generated a lot of research interest for the formulation of nanoparticulate drug delivery systems [18,19]. Poly (ortho ester)'s have the advantage of undergoing controllable degradation. The degradation of polyphosphazenes and the linkage of reactive drug molecules to the polymer backbone are controlled by the side-group modification. Langer and coworkers reported a family of synthetic biodegradable Poly (Polyol Sebacate) (PPS) via the bulk polycondensation reactions of the polyol and sebacic acid monomers [20]. Material properties including the physicochemical and mechanical properties as well as the degradation rates of the obtained PPS can be tuned by altering the reacting stoichiometric ratio of monomers polyol and sebacic acid. Through the assessment of biocompatibility *in vitro* and *in vivo*, PPS polymers were found have comparable biocompatibility to Poly (L-Lactic-co-Glycolic Acid) (PLGA) which is a type of material approved for human use.

Liposome

Liposome which is the most intensively investigated family of particulate carriers consists of highly ordered lipid molecules in a lamellar arrangement that encapsulates a fraction of the solvent in which they are suspended [21]. As a type of natural biomaterials, liposomes are considered as promising and harmless drug carriers that can circulate in the bloodstream for an extended time [22].

For the liposome to act as a useful drug carrier, it should as a minimum be able to retain an encapsulated drug for a sufficiently long time after its administration in order to appropriately alter the pharmacokinetics of the drug. However, there have been major drawbacks existing in the use of liposomes for targeted drug delivery,

most notably due to poor control over drug release from the liposome (i.e., the potential for leakage of the drug into the blood), low encapsulation efficiency and manufacturability at the industrial scale, and poor storage stability [23,24]. Numerous studies have been carried out to meet these challenges and considerable progress has been achieved, as seen from Torchilin's review articles [25,26]. Figure 2 represents the illustrative structure of a new generation of liposomes, which can be tailor-made to carry different types of functional groups with an aim to reach the optimal interplay of various biophysicochemical parameters as denoted by the letters in figure 2.

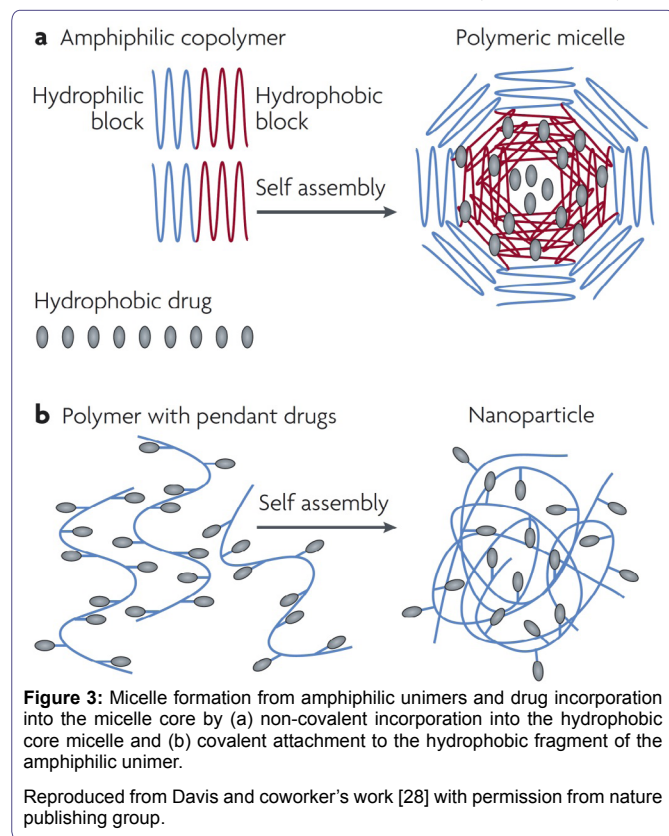


Stimuli-Responsive Amphiphilic Block Copolymers

Stimuli-responsive amphiphilic block copolymers have received much attention due to their various promising potential applications in biomedical fields. Responsive polymeric systems are polymers whose solubility, volume, configuration and conformation can be reversibly manipulated by changes in external stimuli. These are chemical or physical stimuli. The chemical stimuli, such as pH, ionic factors, and chemical agents, will change the interactions between the polymer chains or between the polymer chains and solvents at the molecular level. The physical stimuli, such as temperature, electric or magnetic fields, and mechanical stress, will affect the level of various energy sources and alter molecular interactions at critical onset points. These responses of polymer systems are very useful in biomedical applications such as drug delivery, biotechnology, and chromatography [27]. The pH and temperature-responsive block copolymers are of considerable importance because they can form polymeric micelles, vesicles, or

hollow nanospheres in aqueous media via changing the surrounding environment, and further provide a variety of applications for switchable interfaces, coatings, paints, and adhesives besides areas of biomedicine.

The drug delivery carriers prepared from the block copolymers are obtained by taking advantage of the feature of an amphiphilic self-assembled property, by which a core-shell structured micelle can form and provide a loading space to accommodate mainly hydrophobic drugs in aqueous solution. The drug can be incorporated into the micelle core either by the covalent attachment to the hydrophobic fragment of the amphiphilic unimers or via a non-covalent interaction into the hydrophobic core of the micelle (Figure 3). The nanoscale polymer micelles should exhibit prolonged systematic circulation times and reduced uptake by the mononuclear phagocyte system. Anticancer drugs that are incorporated into core-shell micelles have to show improved stability and efficiency [15].



pH-responsive amphiphilic block copolymers

pH-responsive polymeric systems relying on microenvironment sensors to drive polymer nanoparticles localization are particularly promising for nanobiological applications and have attracted special attention since a large number of pH variations can be found in normal or infected tissues [29]. The development of pH triggered carrier systems can increase the concentrations of the active anticancer drugs within the cancer cells via the efficient release of the drugs from the carriers into the cytoplasm, which thus greatly improves the cure efficacy of chemotherapy for cancer. The adjustment in pH alters the ionic interaction, hydrogen bonding, and hydrophobic interaction, resulting in a reversible microphase separation or self-organization phenomenon [30]. They mainly include three types of copolymers: (1) self-assembly of block

copolymers of tertiary amine methacrylates [31-36], (2) self-assembly of block copolymers having 2-methacryloyloxyethyl phosphorylcholine [37], (3) self-assembly of folate-functionalized block copolymers [38-40].

Tam and coworkers [41] synthesized a pH-responsive Poly (Methacrylic Acid) -b-Poly ((2-Diethylamino) Ethyl Methacrylate) (PMAA-b-PDEAEMA) diblock copolymer via Atom Transfer Radical Polymerization (ATRP) technique using protected group chemistry of tert-butyl methacrylate, followed by hydrolysis under acidic conditions. This copolymer system is believed to have the potential for drug-delivery applications because of the biocompatibility of PMAA and PDEAEMA. PMAA is a weak acid ($pK_a = 5.4$), which can be ionized and becomes soluble at high pH, whereas PDEAEMA is a weak base ($pK_a = 7.3$), which can be protonated at low pH and makes the block hydrophilic polymer. Because both blocks have different pK_a values and different chain lengths, the Hydrophile-Lipophile Balance (HLB) values of the block copolymer at high or low pH values are different. Recently, Tam and coworkers also reported α -Cyclodextrin (α -CD) induced assembly of a double hydrophilic block copolymer Poly (Ethylene Oxide)-b-Poly (Acrylic Acid) (PEO-b-PAA). A vesicular nanostructure was produced with a hydrodynamic diameter of 330 nm, which may have potential applications as a drug delivery vehicle [42].

Rempel and coworkers prepared a type of pH-responsive ellipticine-loaded poly (DEAEMA)-poly (PEGMA) core-shell structured nanosphere with an average particle diameter of 96.2 nm via a two-step semibatch emulsion polymerization technique for the purpose of carrying out, controlled release, and delivery of hydrophobic antitumoral agent ellipticine [43]. DEAEMA and PEGMA represent 2-(diethylamino) ethyl methacrylate and poly (ethylene glycol) methacrylate, respectively. Ellipticine (5,11-dimethyl-6H-pyrido [4,3-b] carbazole) is a natural antineoplastic plant alkaloid with a green fluorescence property, which can be extracted from natural sources including *Ochrosia elliptica*, *strychnos dinklagei* and *Bieckeria vitiensis* [44-46]. The release of ellipticine from core-shell nanospheres at 37°C was found to be a highly pH-responsive and controlled release process. An increase in the acid strength will accelerate the rate of release. The ellipticine-loaded nanospheres can be triggered at pH's of 3, 4, and 5 to achieve a significant ellipticine release of 88% after 98 h, 83% after 98 h, and 79% after 122 h, respectively. The release of ellipticine from the polymer matrix in low pH media was thought to be controlled by the deformation of the polymer matrix and electrostatic repelling force between the protonated ellipticine and poly (DEAEMA) segment. In addition, the PEG corona derived from PEGMA polymers can impart stealth like properties on the nanoparticles, which can enhance the lifetime circulation of nanocarriers.

Temperature responsive block copolymers

Temperature-responsive polymers have also received much attention because of their unique characteristics such as the presence of a critical solution temperature. Critical solution temperature is the temperature at which the phase of polymer and solution (or the other polymer) is discontinuously changed according to their composition. The polymer solution (mostly water) has one phase below a specific temperature depending on the polymer concentration. However, the phase separation occurred above this temperature and the micelle was formed. The polymer generally has a Lower Critical Solution Temperature (LCST): the lowest temperature of the phase-separation

curve on a concentration-temperature diagram (Figure 4). Otherwise, it is called a Higher Critical Solution Temperature (HCST) or Upper Critical Solution Temperature (UCST). Until now, most applications are related to LCST-based polymer systems [27].

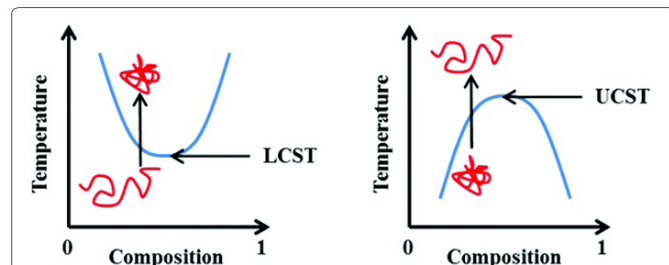


Figure 4: Schematic diagram illustrating the phase transition of polymer binary solution associated with the LCST (Lower Critical Solution Temperature) and UCST (Upper Critical Solution Temperature). Blue line represents the phase separation boundary at which a cloud point is observed.

Reproduced from Phillips and Gibson's work [27] with permission from Royal Society of Chemistry.

Recently, Sugihara and coworkers synthesized a series of random copolymers poly (HOBVE_{1-x}-ran-VEM_x) containing poly (4-hydroxybutyl vinyl ether) and 2-(vinylxy) ethyl methacrylate, and thermo responsive coacervate droplets were obtained [47]. These initially formed coacervate droplets. Slightly above the phase separation temperature with cross-linking by UV irradiation in water to form fine hydrogel microspheres.

pH/temperature/salt multi-responsive block copolymers

This category of polymer systems were defined as a phase transition in response to more than one variable, in particular pH/temperature and salt.

Recently, Lee and coworkers synthesized a novel pentablock copolymer Oligomeric Sulfamethazine (OSM)-b-Poly (ϵ -Caprolactone-co-Lactide) (PCLA)-b-PEG-b-PCLA-b-OSM using Br-PCLA-b-PEG-b-PCLA-Br as a macroinitiator for ATRP, in which Sulfamethazine Methacrylate monomer (SM) was used as a pH responsive moiety. PCLA-b-PEG-b-PCLA was used since it is biodegradable and temperature sensitive, as well as a type of amphiphilic triblock copolymer. The block copolymer solution shows a sol-gel transition in response to a slight pH change over the range of 7.2-8.0 [48].

Li and coworkers reported a type of self-assembled thermo- and pH-responsive polymer micelle from Poly (Acrylic Acid)-b-Poly (n-Isopropylacrylamide) (PAA-b-PNIPAM) using ATRP techniques and Doxorubicin (DOX) was used for entrapment and release experiments [49].

Recent trends aim at developing materials that respond to more than one stimulus or try to broaden the applicability and expand such phenomena to other solvent systems and have given rise to several other types of novel stimuli responsive systems, for example, the redox-mediated reversible micellization of block copolymers. Manners and coworkers reported a type of Polystyrene-b-Polyferrocenylsilane (PS-PFS) block copolymer wherein PFS can be selectively oxidized in a controlled manner [50]. The micellization was induced through monitoring the polarity of the charged PFS segment in the oxidation process. Another example is the incorporation of the light responsive segment into the polymer chains. Zhao and coworkers synthesized a block copolymer composed of a side-chain liquid crystalline azobenzene-containing Polymethacrylate and Poly

(tert-Butyl Acrylate) (PAzoMA-b-PtBA). The reversible changes in the micellar aggregates for both the core-shell micelles and vesicles took place upon irradiation as a result of the reversible *trans-cis* photoisomerization of azobenzene mesogens in PAzoMA [51].

It is worthwhile to note that the polymeric drug delivery types mentioned above sometimes are not used individually, but will be combined to fabricate a better-performing drug delivery system. For instance, Farokhzad and coworkers synthesized PLGA-lecithin-PEG core-shell nanoparticles by a modified nanoprecipitation method coupled with self-assembly for controlled drug delivery through combining the beneficial properties of liposomal and polymeric nanoparticles. These hybrid nanoparticles consist of (a) a PLGA hydrophobic core, (b) a soybean lecithin monolayer, and (c) a hydrophilic PEG shell. These types of hybrid nanoparticles assemble the respective merits of the polymer and liposomes, which may represent a useful controlled release drug delivery system.

Expected Criteria for the Preparation of Polymer Nanoparticles for Drug Delivery

- 1) The size of the particulate drug carriers has been proven to be the primary key in determining their biodistribution. The smaller particle size can dramatically decrease the chances of uptake by macrophages of Reticuloendothelial Systems (RES) and then reduce the accumulation in the liver and spleen. The optimal size of nanoparticles is typically considered to be between 25 and 100 nm [52].
- 2) The Critical Micelle Concentration (CMC) value is expected to be as low as 10^{-3} molar or even lower;
- 3) Better biodistribution of nanoparticles;
- 4) Longer blood circulation period;
- 5) Controlled release profile for the incorporated drug ;
- 6) Good compatibility between the core-forming block and the incorporated drug;
- 7) Coordination of moieties of nanoparticles. In order to prepare "smart" multifunctional pharmaceutical nanocarriers, various chemical moieties were required to provide certain required individual properties via simultaneous attachment on the nanocarriers. Therefore, it is a central challenge on how to optimize the biophysicochemical parameters to work coordinately to reach a desired combination of useful properties.
- 8) A higher loading and encapsulation efficiency toward the aimed drug should be satisfied.

Summary

Drug delivery has accounted for a prominent research aspect of nanomedicine and nanobiotechnology, especially with the continuing discovery of potent and specific new drugs and the increased understanding of disease pathways and the metabolism and pharmacokinetics of drugs *in vivo*. Meanwhile, polymer nanoparticles characterized by stimuli-responsive polymer nanoparticles are playing an increasingly more important role in the delivery of drugs and other pharmaceuticals. Polymer nanoparticle based drug delivery systems can provide extensive macromolecular biochemical diversity and have potential for further modification by means of customized incorporation of various "smart" functionalities that could enable the control release and diagnosis *in vivo*. Future efforts

will focus on how to develop complex “smart” drug delivery systems that can be responsive to biochemical signals or biomarkers commonly present in an extremely low concentration and multi-responsive to several external and intracellular physicochemical stimuli coordinately in an efficient manner. In short, the polymer nanoparticle based drug delivery system has established a mature technology platform to prevent, to treat, and ultimately to cure the diseases at present or as it is emerging.

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